
Multiplex analysis of mitochondrial DNA pathogenic and polymorphic sequence variants.

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Public Summary:

Scientific Abstract:

The mitochondrial DNA (mtDNA) encompasses two classes of functionally important sequence variants: recent pathogenic mutations and ancient adaptive polymorphisms. To rapidly and cheaply evaluate both classes of single nucleotide variants (SNVs), we have developed an integrated system in which mtDNA SNVs are analyzed by multiplex primer extension using the SNaPshot system. A multiplex PCR amplification strategy was used to amplify the entire mtDNA, a computer program identifies optimal extension primers, and a complete global haplotyping system is also proposed. This system genotypes SNVs on multiplexed mtDNA PCR products or directly from enriched mtDNA samples and can quantify heteroplasmic variants down to 0.8% using a standard curve. With this system, we have developed assays for testing the common pathogenic mutations in four multiplex panels: two genotype the 13 most common pathogenic mtDNA mutations and two genotype the 10 most common Leber Hereditary Optic Neuropathy mutations along with haplogroups J and T. We use a hierarchical system of 140 SNVs to delineate the major global mtDNA haplogroups based on a global phylogenetic tree of coding region polymorphisms. This system should permit rapid and inexpensive genotyping of pathogenic and lineage-specific mtDNA SNVs by clinical and research laboratories.

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